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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS : Egan et al.
SERIAL NUMBER : 09/905,188 EXAMINER : Cybille Delacroix-Muirheid
FILING DATE : July 13, 2001 ART UNIT : 1614
FOR : METHODS FOR TREATING FIBROTIC DISEASES OR OTHER INDICATIONS IC

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Commissioner for Patents
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DECLARATION OF HOWARD B. HAIMES UNDER 37 C.F.R. §1.132

I, Howard B. Haimes, of 114 Woodland Street, Natick, MA, declare and state that:

1. I received Ph.D. degree in Biochemical Cytology from Sue Golding Graduate Division of the Albert Einstein College of Medicine, Yeshiva University, Bronx, NY and a M.S. in Biochemical Cytology from Sue Golding Graduate Division of the Albert Einstein College of Medicine, Yeshiva University, Bronx, NY and an M.X. degree in Biology from Long Island University, Brooklyn, NY and a B.S degree in Biology from Union College, Schenectady, NY .

2. I am presently employed by Alteon Inc., 6 Campus Drive, Parsippany, NJ 07054, the assignee of the above-referenced patent application. I have been employed by Alteon Inc. for 1 year.

3. I have reviewed the Final Office Action dated October 6, 2004. I understand that claims 1-4, 7-10 and 12-14 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement.

4. I disagree with the Examiner's assertion that the specification does not support a method of treating, ameliorating or preventing hypertension or systolic hypertension by administering the claimed combination as the Examiner alleges the specification only provides support for the claimed combination thereby only when it is used to treat cardiovascular therapies

(antioxidants), or heart failure, cardiomyopathy or heart attack or atherosclerosis. One of ordinary skill in the art would readily recognize that the essential manifestation of these disorders of which to direct treatment is isolated systolic hypertension. Further, the Examiner refers to Goodman and states the agents recited in page 21, line 23 - page 22, line 11 (*i.e.*, diuretics) are used for treating hypertension. Thus, I submit that based on the state of the art at the time of filing and the disclosure in the specification at page 18, line 21 - page 19, line 31 and page 21, line 23 - page 22, line 11 that one of ordinary skill in the art would readily conclude that at the time the application was filed, Applicants had possession of the invention as claimed.

5. I also understand in reviewing the October 6, 2004 Final Office Action that claims 1-4, 7-10 and 12-14 are rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent 5,853,703 to Cerami ("Cerami") in view of Goodman & Gilman's, The Pharmacological Basis of Therapeutics ("Goodman").

6. I have reviewed the present application in conjunction with the Cerami and Goodman references.

7. I disagree with the Examiner's assertion that any anti-hypertensive agent can be combined with any other anti-hypertensive agent to produce an additive effect in the treatment of hypertension. In fact, several of the oldest and most widely used anti-hypertensive agents (*i.e.*, Methyldopa, Clonidine, Reserpine) are not readily combined with other anti-hypertensive agents to treat hypertension and combinations of these anti-hypertensive agents have numerous detrimental side effects.

8. Using references available on the filing date of the instant application, one of ordinary skill in the art would not reasonably expect that any anti-hypertensive agent could be combined any other anti-hypertensive agent to produce an additive effect in the treatment of hypertension and certainly not to specifically treat isolated systolic hypertension. Further, one of ordinary skill in the art reading the thiazolium disclosure of Cerami which does not specifically teach the administration or formulation of 3-(2-phenyl-2-oxoethyl)-4,5-dimethylthiazolium chloride, would not combine that disclosure with the general anti-hypertension disclosure of

Goodman to reach the specific thaizolium and diuretic species combination of the instant invention to treat isolated systolic hypertension with a reasonable expectation of success.

9. The present invention provides a solution for the long-felt but unsolved need for methods or formulations that safely and specifically treat, ameliorate or prevent isolated systolic hypertension in a subject. Currently, essential hypertension is treated by numerous anti-hypertensive agents (*e.g.*, diuretics, calcium channel blockers, ACE inhibitors, angiotensin II receptor antagonists, etc.). These treatment methods utilizing the traditional anti-hypertensive agents indiscriminately decrease systolic and diastolic blood pressure. Isolated systolic hypertension is quite different from essential hypertension and is defined as systolic blood pressure higher than 160 mm Hg with a diastolic blood pressure of 90 mm Hg or lower. It is the normal or low diastolic pressure that is the defining characteristic that makes isolated systolic hypertension different from essential hypertension. Treatment with traditional anti-hypertensive agents lower the increased systolic blood pressure but concomitantly lowers the already low diastolic blood pressure in subjects with isolated systolic hypertension. This simultaneous lowering of low diastolic pressure leads to the controversial J-curve phenomenon and the compromise of coronary perfusion.

   Increased vascular stiffness and the resulting reduced vascular compliance are the critical factors which underlies the pathogenesis of isolated systolic hypertension. The reduced vascular compliance leads to an increase in pulse pressure and pulse wave velocity, which is associated with an earlier and enhanced reflection of pressure waves from the periphery that results in increase of systolic blood pressure, while the diastolic blood pressure deceases, resulting in increased pulse pressure. Thus, there is a long-felt but unsolved need for methods and formulations which are able to improve vascular compliance which would lower systolic blood pressure without simultaneously lowering diastolic blood pressure in subjects with isolated systolic hypertension.

10. The present invention solves this long felt need by combining hydrochlorothiazide with 3-(2-phenyl-2-oxoethyl)-4,5-dimethylthiazolium chloride which, different than other anti-hypertensive agents that only generally improve vascular compliance, directly reduces vascular stiffness and the resulting reduced vascular compliance. This direct action, along

with decreasing systolic blood pressure, can increase the mean and even the minimum diastolic blood pressure. Thus, I submit that methods and formulations combining a specific compound (3-(2-phenyl-2-oxoethyl)-4,5-dimethylthiazolium chloride) that directly decreases increased vascular compliance with a specific general anti-hypertensive diuretic (hydrochlorothiazide) solve a long-felt but unsolved need in the art by decreasing increased systolic blood pressure without simultaneously decreasing already low diastolic pressure thus avoiding the dangerous J-curve phenomenon and the compromise of coronary perfusion in patients.

11. I further declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001 and that willful false statements may jeopardize the validity of this application and any patent issuing therefrom.

Howard B. Haimes

Signed at Parsippany, NJ

this 22nd day of February, 2005